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The single or dual administration of the gonadotropin-releasing hormone antagonist Cetrorelix* in an in vitro fertilization-embryo transfer program

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Objective: To assess the ability of a GnRH antagonist (Cetrorelix, Asta Medica AG, Frankfurt, Germany) to prevent premature LH surges in an IVF-ET program using a simple protocol with one or two administrations.

Design: Controlled ovarian hyperstimulation was carried out in 17 women with three ampules a day of hMG, starting on day 2 of the menstrual cycle. A dose of 5 mg of Cetrorelix was administered when plasma E_2 levels were between 150 and 200 pg/mL (conversion factor to SI unit, 3.671) per follicle of ≥14 mm. A second injection was performed 48 hours later if the triggering of ovulation was not decided in the meantime.

Results: Six patients received one injection and 11 patients received two administrations. Plasma LH levels showed a marked decrease and remained low after the administration of the GnRH antagonist. In six patients, the first administration of Cetrorelix was performed when a significant rise in LH plasma level was present. Even in these patients the GnRH antagonist was able to prevent an LH surge. The tolerance of the product was good. Six clinical pregnancies were obtained, of which four are ongoing (25% per ET). Two ongoing pregnancies were obtained after the transfer of a frozen-thawed embryo (35.3% per retrieval).

Conclusions: The GnRH antagonist Cetrorelix in a simple, unique or dual administration, protocol was able to prevent premature LH surge in all of the 17 patients studied. If these results are confirmed by larger, randomized studies, the good tolerance and efficacy that we observed suggest a bright future for this product in assisted reproductive technologies. Fertil Steril 1994;62:468–76

Key Words: In vitro fertilization, GnRH antagonist, pregnancies

The ideal controlled ovarian hyperstimulation (COH) for IVF-ET requires the absence of a premature surge in LH levels, thus reducing the risk of cycle cancellation. It also enables the advance scheduling of the cycles to be able to organize IVF-ET programs.

For some of these purposes, GnRH agonists (GnRH-a) have been used in COH to prevent a premature increase in plasma LH and P levels reported in as much as 25% of patients (1). When follicular maturation is not fully attained, premature LH surges and P elevation can have deleterious effects on the quality of oocytes and the endometrium and thereby on pregnancy rates (PRs) (2–4). However, GnRH-a present several disadvantages, namely, a

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period of 1 to 3 weeks may be necessary for desensitization. The use of these substances generally increases the dose of hMG needed. This higher dose of hMG increases the risk of ovarian hyperstimulation syndrome (OHSS), although the relationship between the dose of hMG and the OHSS is not perfectly understood. Other disadvantages of GnRH-a include side effects (hot flushes, vaginal dryness, irritability, and dysfunctional bleeding) that arise as a consequence of the resulting low E_2 levels and can be poorly tolerated by the patients. Nevertheless, GnRH-a also present certain advantages, including a higher number of embryos and the ability to schedule and organize the IVF-ET activity. These factors have led to their wide use in IVF-ET programs; in France, in 1991, 88% of the IVF-ET cycles used GnRH-a (5).

Gonadotropin-releasing hormone antagonists are competitive inhibitors of GnRH receptors. Their administration rapidly decreases gonadotropin secretion (6), delays LH surges (7–9), and prevents premature ovulation and luteinization in COH (10). The recent development of new, potent, and safer antagonists with longer half-lives, high potency, and low histamine release (11) have made GnRH antagonists available for clinical use.

The aim of this study was to assess, in an IVF-ET program, the ability of one of these new GnRH antagonists (Cetrorelix, Asta Medica AG, Frankfurt, Germany) (12) to prevent premature LH surges during COH. The results were compared with patients treated with GnRH-a in our center. A very simple regimen for antagonist administration is used, in which only one or two injections are required in the late phase of COH. The toxicity and tolerance of the product were also evaluated.

MATERIALS AND METHODS

Ethics

All couples were required to sign a statement of informed consent. The study was conducted according to the French Huriet law on biomedical studies and was approved by the Ethical Committee of University Paris-Sud.

Subjects

This study included 17 healthy women between the ages of 28 and 37 years (mean ± SD, 31.8 ± 2.7 years), with regular menstrual cycles (26 to 32 days), tubal factor related infertility, no more than two previous IVF-ET attempts, and normal weight (±20% of the reference weight according to the Metropolitan Insurance table). All the semen parameters were normal (according to World Health Organization [WHO] criteria).

Study Protocol

Patients were monitored during the menstrual cycle preceding the IVF cycle. Plasma E_2, FSH, LH, and P levels were sampled on day 21 of the cycle to confirm normal luteal activity. Preceding admission of a subject in the study, blood pressure, pulse rate, gynecological examination, hematological, biochemical, and urine analyses were performed. An ultrasound (US) examination was also performed to detect any abnormalities in the uterus or ovaries.

The COH was carried out with three ampules of hMG (225 IU) every day, starting on day 2 of the cycle. Follicular maturation was assessed with daily vaginal US and plasma E_2, LH, FSH, and P levels, measured from day 7 of the cycle until 6 days after the last administration of the antagonist.

The GnRH antagonist used in this study was the Cetrorelix (SB-75; Ac-D-Nal(2)[1], D-Phe(4Cl)[2], D-Pal(3)[3], D-Cit[6], D-Ala[10]) (Asta-Medica AG). Toxicologic and teratologic studies carried out on pregnant rates and rabbits have not revealed any adverse side effects. The Cetrorelix was administered subcutaneously in the anterior abdominal wall. Before injection, lyophilized Cetrorelix was dissolved in 9% saline to a final concentration of 1 mg/mL. Local and systemic tolerance to the drug was assessed by physical examination until 1 hour after the antagonist injection. Cetrorelix was first administered at a dose of 5 mg when the plasma E_2 level were between 150 and 200 pg/mL (conversion factor to SI unit, 3.671) per follicule of ≥14 mm, when an imminent LH surge is most feared. A second dose was injected 48 hours later if the triggering of ovulation was not decided in the meantime (Fig. 1).

Triggering of ovulation was achieved with the administration of 10,000 IU of hCG (Gonadotrophine Chorioniques "Endo"; Organon, St. Denis, France) and was decided when the leading follicle attained 18 to 20 mm, with E_2 values indicating satisfactory follicular maturation (E_2 > 920 pmol/mL per follicle; range of E_2 levels: 1,798 to 11,377 pmol/mL). Oocyte retrieval was performed 36 to 40 hours later, under vaginal US guidance. Oocytes were inseminated 3 to 5 hours later with 4,000 mobile sperma-

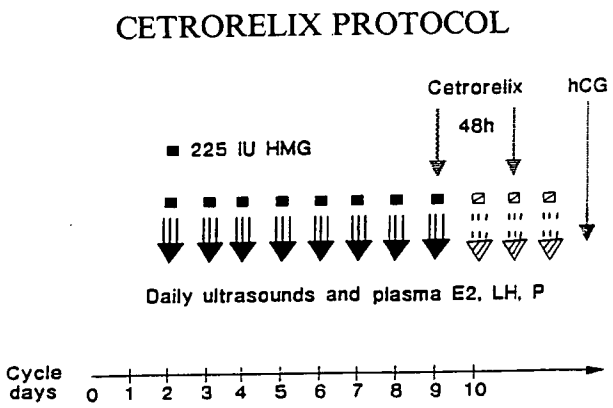

Figure 1 Cetrorelix administration protocol.

tozoa in microdroplets of B2 Medium (A.P.I. Biomerieux, 38390 Matalieu, France) under oil, with 5% CO_2 at 37°C.

Transfers were performed 48 hours after oocyte collection using a Frydman catheter (CCD Laboratories, Paris, France). The luteal phase was supported by daily vaginal administration of 300 mg micronized P (Utrogestan; Besins Iscovesco Pharmaceuticals, Paris, France), started 4 days after hCG administration.

Hormone Assays

Plasma P was measured by RIA using a ^{125}I Progesterone Coatria kit (Bio-Mérieux, Marcy L'Etoile, France). Sensitivity was 0.16 nmol/L. Intra-assay and interassay CVs were, respectively, 8% and 11% for P. Plasma E_2 was determined by an immunometric technique, with a sensitivity of 51.39 pmol/L using an Estradiol-60 Amerlite kit from Kodak Clinical Diagnostics (Les Ulis, France) and with intra-assay and interassay coefficients of variation (CVs) of 8% and 9%, respectively. Plasma FSH and LH were similirarly measured by an immunometric technique using an Amerlite kit from Kodak Clinical Diagnostics; with intra-assay and interassay CVs of 5% and 7% for FSH and 7% and 9% for LH, respectively. Sensitivity was 0.05 mIU/mL (conversion factor to SI unit, 1.00) for FSH and 0.12 mIU/mL (conversion factor to SI unit, 1.00) for LH.

Statistical Analysis

Statistical analysis of our data was performed using one-way analysis of variance or Student's *t*-test for the comparison of means. Comparison of percentages was performed with the χ^2 test. A $P < 0.05$ was considered as statistically significant.

RESULTS

Cetrorelix Administration

Six patients received one single injection of Cetrorelix and 11 patients received two injections at 48 hour intervals according to the intensity of the ovarian response to COH. The mean day of the first Cetrorelix administration (day 0) was 9.6 ± 0.6. All patients treated with a single injection of Cetrorelix received hCG 36 hours later, except for one patient in whom hCG was inadvertently administered 72 hours after Cetrorelix (mean day of hCG administration 11.0 ± 0.6). In the remaining 11 patients, hCG was administered within 2 days of the last Cetrorelix administration (mean day 11.7 ± 0.9).

Hormonal Profile During COH

Patients Who Received a Single Antagonist Injection

Luteinizing Hormone Profile. The plasma LH profile during COH with hMG and Cetrorelix is depicted in Figure 2. In all patients (n = 6), plasma LH levels showed a marked decrease after the first injection of Cetrorelix (day 0) from 5.5 ± 4.6 mIU/mL (mean ± SD) on day 0 to 0.2 ± 0.1 mIU/mL on day +1 ($P < 0.0002$). Plasma LH remained constantly low during the next 5-day observation period (the mean LH level of days +2, +3, +4, +5, and +6 was 0.13 ± 0.10 mIU/mL).

Follicle-Stimulating Hormone Profile. Follicle-stimulating hormone levels before and after Cetrorelix administration are illustrated in Figure 2. In all 17 patients, plasma FSH levels decreased significantly after the first Cetrorelix administration from 14.6 ± 1.8 mIU/mL (day 0) to 13.2 ± 2.1 mIU/mL 24 hours later (day +1) ($P < 0.004$). In the six patients who received a single injection of Cetrorelix, FSH levels continued to fall progressively from day +1 on, after hCG administration 24 hours after Cetrorelix injection (day +1).

Estradiol Profile. The E_2 profile of patients who received a single antagonist injection is shown in Figure 2. A subtle decrease in plasma E_2 levels was observed 24 hours after the first Cetrorelix administration (1,774 ± 481 versus 1696 ± 521 pg/mL), although this decrease did not attain statistical significance.

Progesterone Profile. The plasma P profile is exposed in Figure 2. Plasma P levels remained unaltered after the first Cetrorelix administration (0.72 ± 0.36 μg/mL on day 0 and 0.65 ± 0.58 μg/mL [con-

version factor to SI unit, 3.18] on day +1). On the other hand, plasma P levels increased progressively after hCG administration, reaching levels of 49.50 ± 12.14 μg/mL 4 days after hCG administration.

Patients Who Received Two Antagonist Injections

Luteinizing Hormone Profile. The plasma LH profile during COH with hMG and Cetrorelix is depicted in Figure 3. No difference was found in LH levels between patients (n = 11) who received one or two injections of Cetrorelix (mean LH levels of days +1, +2, +3, +4, +5, and +6 was 0.18 ± 0.15 versus 0.11 ± 0.06 mIU/mL, respectively).

Follicle-Stimulating Hormone Profile. The FSH profile from patients who had two Cetrorelix injections is depicted in Figure 3.

In the 11 patients who received two injections of Cetrorelix, plasma FSH increased significantly ($P < 0.002$), reaching levels not different from those observed just before the first Cetrorelix administration (day 0) 24 hours later. Subsequently, after the second Cetrorelix injection and discontinuation of hMG, a progressive and significant fall in plasma FSH levels ($P < 0.04$) was observed in these patients. This decrease is comparable to that observed after the first Cetrorelix administration in the single-injection group and coincides with discontinuation of hMG and hCG administration.

Estradiol Profile. Similarly to the patients who received one injection, a transient pause in the increase of E_2 was observed after the first antagonist administration, as shown in Figure 3 (1,546 ± 645 versus 1,465 ± 676 pg/mL). The second injection did not affect the progressive increase in E_2 levels.

Progesterone Profile. The P profile of patients who received two injections is shown in Figure 3. Plasma P levels remained unaltered after the second antagonist administration and P reached the level of 52.97 ± 23.70 μg/mL 4 days after hCG administration.

Patients With a Significant LH Increase Before Cetrorelix Administration

In six patients, a significant increase in LH levels exceeding 180% was observed on day 0 (9.4 ± 5.2 mIU/mL), with respect to values observed on the preceding days (mean LH levels on days −1, −2, and −3 was 2.0 ± 1.3 mIU/mL) ($P < 0.01$). Interestingly, even in these patients, LH levels showed a drastic decrease and subsequent low levels after the first Cetrorelix administration (mean LH levels of days +1, +2, +3, +4, +5, and +6: 0.14 ± 0.07 mIU/mL).

In Vitro Fertilization-Embryo Transfer Results

The IVF-ET results of the study are presented in Table 1. The total number of hMG ampules required to achieve COH was 27.7 ± 4.2 (mean ± SD). The number of mature oocytes obtained was 7.1 ± 3.5, and the number of embryos available for transfer was 6.1 ± 3.9. Sixteen patients underwent ET, with a mean of 2.6 ± 0.8 embryos transferred, because no embryos were obtained in one patient. Two biochemical and six clinical pregnancies were obtained (37.5% per ET), of which four are ongoing (25% per ET). In addition, two patients have an ongoing pregnancy after the replacement of frozen embryos obtained during the antagonist cycle. The number of ongoing pregnancies per retrieval is therefore six (35.3%), including the successful frozen-thaw transfer. Concerning the group of patients who received the Cetrorelix administration after a significant rise in LH, the fertilization rate (83.0%), calculated on the number of mature oocytes, was not different from the fertilization rate of the rest of the patients (81.6%). Two pregnancies, one of which miscarried, were obtained in this group.

Table 1 also includes the results of a group (not matched) of 149 IVF-ET cycles carried out in our institution in 1992 (Olivennes F, unpublished data). These cycles were selected according to the same patient inclusion criteria retained in this GnRH antagonist study. All these patients underwent COH with an association of long-acting GnRH-a, administered in the early follicular phase, and hMG, started after desensitization (so-called "long protocol").

DISCUSSION

The role of GnRH during the LH surge is now well established both in animals and in humans. A significant preovulatory GnRH surge concomitant to the LH surge has been observed in ewes (13) and in monkeys (14). In women, LH surges have been postponed by antagonist administration (9, 15, 16). These studies support the concept that endogenous GnRH is needed for the E_2-induced LH surge.

This study clearly shows the efficacy of a single or dual administration of a GnRH antagonist (Cetrorelix) in eliminating the risk of endogenous LH surges in COH inasmuch as one or two injections of

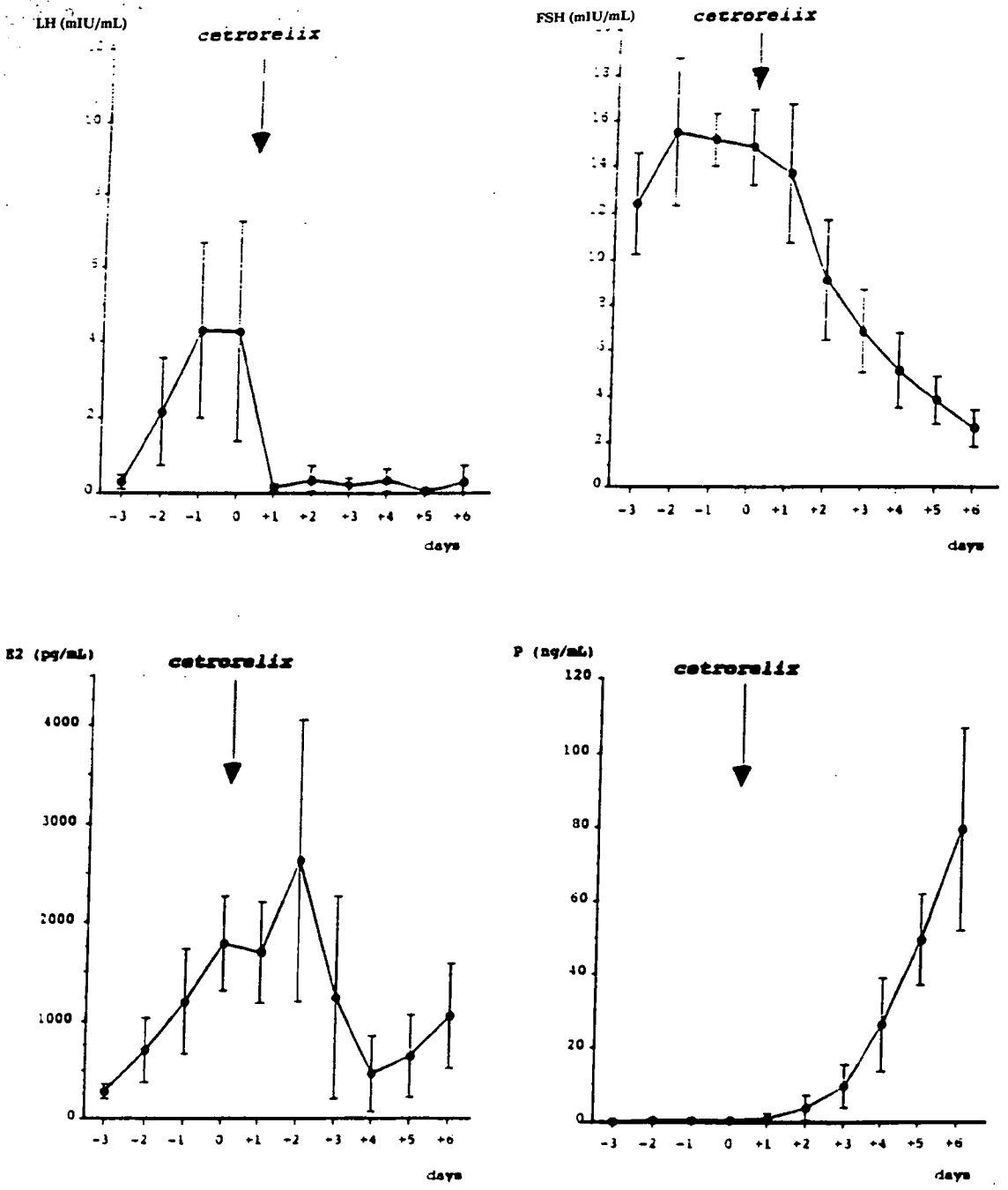

Figure 2 Hormonal profiles of patients who received one injection of antagonist.

5 mg of this drug were successful in preventing a premature LH surge in the 17 patients studied. These results are consistent with those of previous studies established in spontaneous cycles (7, 8, 17, 18) and of our previous study in COH with the GnRH antagonist Nal-Glu (10).

In the six patients (35.3%) of this study in whom LH levels had started to rise significantly, Cetrorelix also induced a drastic decrease in LH levels, which remained low until hCG administration. In this group, the IVF-ET results in terms of number of oocytes, fertilization rate, embryo numbers, and PRs (30% per ET) were not statistically different from the rest of the patients. This increase in LH

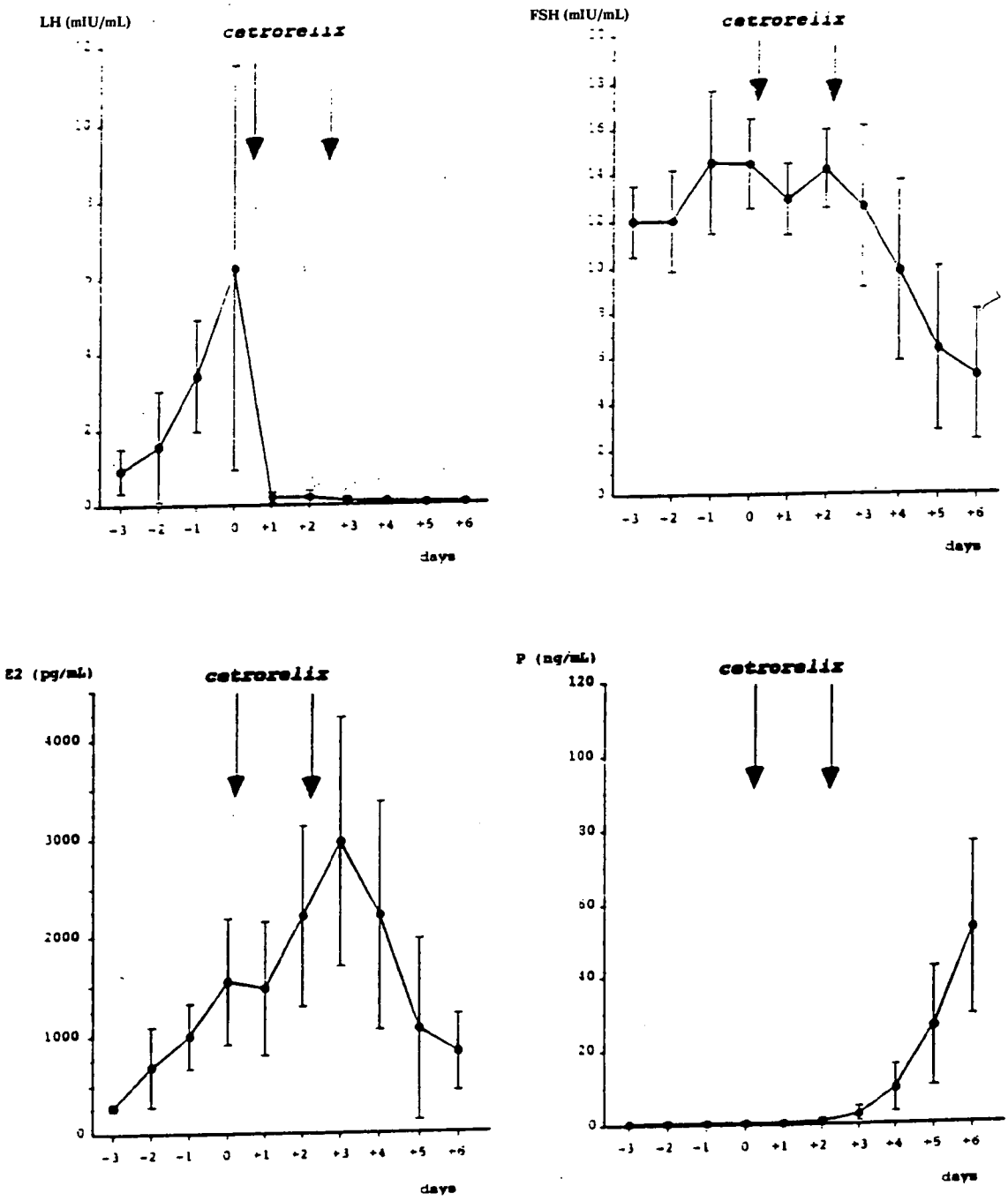

Figure 3 Hormonal profiles of patients who received 2 injections of cetrorelix.

could be attributed to the high E_2 levels resulting from the high dose of hMG given to these young women with tubal infertility and/or to the fact that the first antagonist administration was probably performed too late in the follicular phase.

In the group of patients who received two injections of antagonist, the LH levels did not decrease after the second administration. This phenomenon can be explained by the extremely low levels of LH attained after the first injection. We also failed to observe a rise in LH levels in the 48-hour interval preceding the second injection, including in the patient who inadvertently received hCG 72 hours after the last Cetrorelix injection. These and other

Table 1 IVF-ET Results

	Antagonist	Agonist*
HMG (ampules)†	27.7 ± 4.2‡	38.3 ± 15.4
Oocytes†	7.1 ± 3.5	8.4 ± 5.2
Embryos†	6.1 ± 3.9	6.0 ± 4.2
Fertilization rate (%)	85.9	71.1
Embryo transferred†	2.6 ± 0.8	2.6 ± 0.8
Cycles	17	144
Transfers	16	131
Clinical pregnancies	6	48
Clinical pregnancies/cycle (%)	35.3	33.3
Clinical pregnancies/transfer (%)	37.5	36.6
Ongoing pregnancies	4	38
Ongoing pregnancies/transfer (%)	25.0	29.0

* Long-acting agonist started in the early follicular phase and hMG, 300 IU/d, started after desensitization (unpublished data).

† Values are means ± SD.

‡ Significantly different from women with agonist IVF-ET cycles ($P < 0.001$).

observations conducted in spontaneous cycles (19) suggest the possibility of a long effect of the first injection, which would have allowed us to wait more than 48 hours for the second one.

Similarly to LH, plasma FSH levels decreased, although to a lesser extent than LH, as already described in the literature (18, 20), suggesting that GnRH antagonists suppress more immunoreactive LH than immunoreactive FSH levels. The situation is less clear in terms of bioactive FSH which has been reported to be more rapidly suppressed (21). In addition, this moderate decrease can be partially explained by the exogenous FSH present in the hMG ampules. This can explain the slight increase of the FSH in the group of patients who received two injections.

The transient break in the hMG-induced increase in plasma E_2 levels may correspond to the fall observed in the LH-controlled androgen production after the first Cetrorelix injection.

We could not analyze the luteal phase P secretion because micronized P was systematically administered from the day of the transfer on. In our study with Nal-Glu (10), the patients studied had a normal luteal phase, indicating that P intake may not be necessary. However, this P supplementation was decided because of the higher potency of Cetrorelix compared with Nal-Glu.

Concerning the IVF-ET results, the number of hMG ampules (27.7 ± 4.2) was lower ($P < 0.001$) than the mean number of vials administered in a similar (but not matched) population treated with COH protocols, including GnRH-a (38.3 ± 15.4) (Table 1). The oocytes collected, embryos obtained, and fertilization rates were comparable to the results obtained in our IVF-ET program for the patients treated with long acting GnRH agonist protocols (Table 1). The clinical pregnancy rate per cycle (35.3%) and per transfer (37.5%) are also satisfactory, with 4 of these pregnancies being achieved after >20 weeks of amenorrhea. Of the 17 patients, four patients had frozen embryos and attempted frozen-thawed ET, two of which resulted in ongoing pregnancies. The total number of ongoing pregnancies per retrieval is therefore 6 of 17 (35.3%).

Different procedures for antagonist administration have been used to postpone or suppress LH surge. In spontaneous cycles, Ditkoff et al. (17) used Nal-Glu during 3 consecutive days, delaying the treatment as close as 2 days before the expected LH surge. The same compound (Nal-Glu) was used by Dubourdieu et al. (15) and Frydman et al. (9), who used 10 mg/d for 1 to 5 days. In COH, Cassidenti et al. (22) administered the GnRH antagonist (Nal-Glu) daily from the beginning of the follicular phase and until follicles reached 14 to 16 mm. Frydman et al. (10) used a shorter protocol, similar to the one used in this study, but with Nal-Glu. The antagonist was administered when serum E_2 levels exceeded 600 pg/mL with a repeat administration 48 hours later. Diedrich et al. (23) used also the Cetrorelix with daily administration of 1 mg, started on day 7 of the COH and administered until the triggering of ovulation.

Our present results are promising in term of the use of GnRH antagonists in assisted reproductive technologies. However, until recently, the antagonists used had a number of drawbacks, namely a short biological life, high histamine release, and relatively low potency (24).

The protocol of antagonist administration employed in this study was simple to use, with the need for a second injection being debatable for the majority of patients. Avoiding premature LH surges with a single injection, which could be administered on a fixed day of the stimulation protocol (e.g., day 8), would simplify considerably the management of IVF cycles. Moreover, we observed almost no side effects, with the exception of a transient local erythema at the injection site in two patients. The product therefore seems to be well tolerated. This was particularly obvious in patients who had had previous IVF attempts with GnRH-a using long-acting preparations. In our study, Cetrorelix was much better accepted than the GnRH-a long proto-

col by the patients. This observation, albeit very subjective, must be taken into account. The use of GnRH-a also has been proposed in short and "ultrashort" protocols, but the results of these protocols remain controversial (25). The drastic effect of the 5-mg dose also suggest that a smaller dose should be tested.

These products could also be of interest for their use in ovulation induction (without IVF-ET), e.g., patients with polycystic ovarian syndrome; in case of an excessive response to gonadotropins, the mechanism of action of GnRH antagonists would allow the triggering of ovulation with native GnRH or with GnRH-a to reduce the risk of OHSS, observed with hCG under these circumstances.

In conclusion, premature LH surges lead to a high rate of cancelled cycles in IVF programs in which ovarian stimulation is conducted without GnRH-a. The use of a new potent GnRH antagonist, Cetrorelix, was able to prevent an LH surge in all of the 17 patients studied, this effect being obtained with a single or dual injection of the antagonist. In the group of patients who received two administrations, the second injection could probably have been omitted in some of them. In addition, this regimen allows a reduction in the dose of hMG and, therefore, probably in the risk of hyperstimulation syndrome. Our results need to be confirmed by larger, randomized studies, but the simplicity of administration and the apparent tolerance and efficacy in preventing premature LH surges suggest a bright future for this compound in assisted reproductive technologies.

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